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2004-003.A102.US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Dominique Charmot et al.
Serial No.: 10/813,872
Filed: March 30, 2004
Confirmation No.: 5573
For: ION BINDING COMPOSITIONS
Examiner: Micah Paul Young

Art Unit: 1618

October 4, 2010

APPEAL BRIEF

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This is an appeal from the final rejection of the claims of the above-referenced application made in the Office action dated May 4, 2010. A Notice of Appeal was filed on August 3, 2010.

I. REAL PARTY IN INTEREST

The real party in interest in connection with the present appeal is Relypsa, Inc., the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

Appellants are appealing U.S. Application No. 10/814,749 that has an identical specification and includes claims directed to core-shell particles. This appeal is pending, the application was received by the Board from the Technology Center on September 7, 2010, and was assigned Appeal No. 2010-011651. Applicants are uncertain whether this pending appeal will directly affect or be affected by, or have a bearing on, the Board's decision in the present appeal.

III. STATUS OF CLAIMS

Claims 1, 17, 22-24, 31, 32, 45-56, 58-65 and 67-69 are pending. Claims 2-16, 18-21, 25-30, 33-44, 57, and 66 are canceled. A copy of the pending claims appears in the Claims Appendix of this Brief.

Claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 5,824,339) and Bogentoft (EP 0 040 590).

Applicants appeal the rejections of claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 under U.S.C. § 103(a) as being unpatentable.

IV. STATUS OF AMENDMENTS

No amendments were made after the final Office action. The pending claims are set out in the Claims Appendix.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is generally directed to a pharmaceutical composition comprising core-shell particles.

Independent claim 1 is directed to an oral or rectal[1] pharmaceutical composition comprising core-shell particles and a pharmaceutically acceptable excipient. The core-shell particles comprise a core component and a shell component[2] wherein the core component comprises a potassium-binding cation exchange polymer[3] and the shell component comprises a crosslinked synthetic polymer being produced by a free radical polymerization of an ethylenic monomer selected from the group consisting of acrylic, methacrylic, styrenic, dienic, and vinylic and combinations thereof.[4] The shell component is also essentially not disintegrated during residence and passage through the gastrointestinal tract of an animal subject.[5]

Independent claim 45 is directed to a method of treating an animal subject suffering from renal insufficiency or renal failure and comprises administering an effective amount of the pharmaceutical composition of claim 1 to an animal subject in need thereof.[6]

Independent claim 68 is directed to an oral pharmaceutical composition comprising a pharmaceutically acceptable excipient and core-shell particles, said core-shell particles comprising a core component and a shell component with the core component comprising a potassium-binding cation exchange polymer,[7] the shell comprising a crosslinked polymer or polymer produced by polymerization of an acrylic or methacrylic monomer[8] wherein said shell component is about 0.005 microns to about 20 microns thick,[9] the core-shell particle is about 200 nm to about 2 mm in size,[10] and the shell component being essentially not disintegrated in the gastrointestinal tract of an animal subject.[11]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants appeal the rejection of claims 1, 17, 22-24 31, 32, 45-56, 58-65 and 67-69 under 35 U.S.C. § 103(a) as being unpatentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590).

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[1] *See* specification at paragraph [0076].
[2] *See* specification at paragraph [0008].
[3] *See* specification at paragraph [0056].
[4] *See* specification at paragraph [0039].
[5] *See* specification at paragraph [0014].
[6] *See* specification, original claims 42 and 44.
[7] *See* specification at paragraph [0056].
[8] *See* specification at paragraph [0039].
[9] *See* specification at paragraph [0046].
[10] *See* specification at paragraph [0047].
[11] *See* specification at paragraph [0014].

VII. ARGUMENT

Claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 are patentable over Notenbomer (EP 0 730 494) in view of Macek (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a).

Claim 1

Reconsideration is respectfully requested of the rejection of claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 as unpatentable over Notenbomer (EP 0 730 494) in view Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a). Independent claims 1, 45, and 68 are described in detail above, claims 51, 52, and 53 further require a vinylic or an acrylic or methacrylic monomer. The Office asserts that it would have been obvious "to combine the coatings of the '960 (Macek) patent on to the '494 (Notenbomer) patent since both solve the problem of binding ions in the gastrointestinal tract."[12]

Notenbomer discloses methods and particles for binding monovalent cations. The Notenbomer particles have a nucleus and a coating; the nucleus contains a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and crosslinked polyethyleneimine. Generally, these particles are disclosed for treating hypertension. Notenbomer does not disclose any of the specific coatings required by claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69.

Macek et al. disclose polymers used to remove bile acids; the polymers disclosed are polystyrene resins crosslinked with divinyl benzene and functionalized through chloromethylation of the aromatic rings and replacement of the chlorine atom with a tertiary amine such as trimethyl amine to form a trimethyl ammonium group attached to the aromatic rings. Thus, the polymers are amine polymers that can be coated with carboxypolymethylene crosslinked with polyallyl sucrose or an acrylic acid polymer crosslinked with polyallylsucrose. Macek described the typical coating agent of Carbopol 934 as dispersing "readily in water to

[12] *See* Office action dated May 4, 2010 at page 5.

yield a solution of low viscosity, which is transformed into a clear, stable gel on neutralization."[13]

The Bogentoft patent is directed to methods of coating particles in order to direct drug compounds to the lower part of the intestine. Bogentoft does not disclose a shell that is non-disintegrated because its coating comprises a carboxylic acrylic polymer that is soluble above pH 5.5, and the gastrointestinal tract is above pH 5.5. Bogentoft describes a shell which allows for the release of anti-inflammatory drugs to the colon or ileum,[14] or alternatively provides for the release of an anion exchanger such as cholestyramine in the lower colon.[15]

The PTO is arguing that it would have been obvious to one of ordinary skill in the art to choose the specific polymeric coatings of Macek from millions of possible available coatings "since both patents solve the same problem of binding ions in the gastrointestinal tract."[16] The Office further states that it would have been "obvious to apply the acrylic polymer [of Bogentoft] to the ionic exchange resin of the combination in order to provide an even and stable formulation that allowed ions to pass through."[17]

Applicants submit that the above rejection is in error for the following reasons.

As is well known, the determination of whether a claim is obvious within § 103(a), depends on at least four underlying factual issues set forth in *Graham v. John Deere Co. of Kansas City*[18]: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any relevant secondary considerations. In April 2007, the Supreme Court affirmed the *Graham* analysis as the framework for determining obviousness.[19]

In addressing the scope and content of the prior art, references are not pertinent to an obviousness inquiry if they are not from analogous art.[20] A reference is analogous art if: (1) the reference is from the same field of endeavor, regardless of the problem addressed, or (2) the reference is not within the inventor's field of endeavor, yet it is reasonably pertinent to the particular problem addressed by the inventor.

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[13] U.S. Patent No. 3,499,960, column 3, lines 15-17.
[14] *See* EP App. No. 0 040 590, p. 1, ln. 28-31.
[15] *Id.* at p. 2, ln. 1-5
[16] *See* Office action dated May 4, 2010 at page 8.
[17] *Id.* at page 4.
[18] 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966).
[19] *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007).
[20] *In re Clay*, 23 U.S.P.Q.2d 1058, 1060 (Fed. Cir. 1992).

In *Clay*, the PTO asserted that the claimed invention and the Sydansk reference were analogous art because they were part of a common endeavor of "maximizing withdrawal of petroleum stored in petroleum reservoirs."[21] Sydansk taught the

> use of a gel in unconfined and irregular volumes within generally underground natural oil-bearing formation to channel flow in a desired direction; Clay teaches the introduction of gel to the confined dead volume of a man-made storage tank.[22]

However, the Federal Circuit disagreed with the Office and held that Clay's field of endeavor was "*storage* of refined liquid hydrocarbons" and Sydansk's invention was directed to the "*extraction* of crude petroleum."

When a reference has the same purpose as the claimed invention, it relates to the same problem, and that fact supports use of that reference in an obviousness rejection; but when a reference has a purpose different from that to which the claimed invention is directed, one skilled in the foreign art might or might not have reason to modify for some alien purpose; but the artisan concerned with the inventor's problem would have no motivation to consider the reference at all, as a candidate for modification or otherwise.[23]

The purpose of the Notenbomer patent is to develop core-shell particles that can bind sodium preferentially over divalent cations.[24] Although Notenbomer states that the core-shell particles can be used to remove potassium from a gastrointestinal tract, binding and removing sodium and potassium from the gastrointestinal tract are very different problems. For example, there are many differences between binding sodium and potassium even though they are similar target ions. These differences include variances in the relative and absolute amounts of sodium and potassium along the gastrointestinal tract; the amounts of sodium and potassium depending upon the condition suffered by the patient; and the selectivity of a cation exchange polymer for sodium and potassium ions.

The amount of sodium as compared to the amount of potassium available for binding will be different because the relative and absolute amounts of sodium and potassium in the contents of the gastrointestinal tract change depending on location (e.g., distance from the stomach). Notenbomer recognizes this difference by relying on sodium being present in high amounts in comparison to the relatively low concentration of potassium (p. 3, lines 3-6). Also, Fordtran et

[21] *Id.*
[22] *Id.*
[23] *Id.*
[24] *See* U.S. Patent No. 5, 833,854 at column 1, lines 62-64.

al.[25] studied the sodium and potassium concentrations in the contents of the upper GI after different meals (see especially Figs 2, 4 and 10) and found that at the end of the ileum, the sodium concentration is relatively high, whereas the potassium concentration is relatively low. However, at the end of the gastrointestinal tract, the contents have a relatively high potassium concentration and a relatively low sodium concentration.[26]

Further, when a subject suffers from hyperkalemia, the body compensates for the high intracellular potassium concentration in various ways, and thus, the amount of sodium or potassium found within the gastrointestinal tract in hyperkalemic patients can be much different from the sodium and potassium concentrations of healthy people or patients suffering from various diseases. For example, clinical evidence shows that hyperkalemic patients with renal dysfunction or chronic kidney disease (CKD) who are not on dialysis increase potassium excretion in the terminal colon, as described in the review by Musso.[27] Specifically, Musso states:

> During CKD, the small intestine makes a greater contribution to potassium excretion than it does under normal conditions. Intestinal potassium excretion rises during chronic renal failure and the body can eliminate an additional 10–20 mmol of potassium by this route. Colonic potassium secretion begins to adapt when glomerular filtration is reduced to around one-third of normal and when renal failure is advanced, this route may account for as much as 30–70% of total potassium excretion.

This means that depending on the patient's condition, the same cation-binding polymer can have a different effect on potassium and sodium concentrations in the body. Patients on drugs that affect potassium secretion, such as potassium sparing and non-potassium sparing diuretics, will have various perturbations in their sodium/potassium balance that may affect potassium and sodium availability in the gastrointestinal tract. Thus, these patients could also experience a different effect on potassium and sodium concentrations in the body upon administration of a cation-binding polymer.

The reasoning that a skilled person would have been motivated to combine the Notenbomer and Macek teachings to produce a stable coated cation exchange resin can be

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[25] J.S. Fordtran et al., "Ionic Constituents and Osmolality of Gastric and Small-Intestinal Fluids after Eating," *Am. J. Digestive Dis.* **1966**, *11(7)*, 503.

[26] O. Wrong et al., "*In Vivo* Dialysis of Faeces as a Method of Stool Analysis," *Clin. Sci.* **1965**, *28*, 357-375 (see Figures 2 and 4).

[27] C.G. Musso, "Potassium Metabolism in Patients with Chronic Kidney Disease (CKD), Part I: Patients Not on Dialysis (Stages 3-4)," *International Urology and Nephrology* **2004**, *36*, 465-468.

compared to that in *Clay*, where the PTO asserted that the claimed invention and the Sydansk reference were of a common endeavor because they were directed to "maximizing withdrawal of petroleum stored in petroleum reservoirs."[28] But in this case, the PTO articulates no reason why the Macek patent is analogous art to either the invention or Notenbomer. Applicants' endeavor is development of oral potassium binders that have increased selectivity by using a coating of the claimed thickness.[29] Macek is directed to anion exchange cores with negatively charged shells that bind bile acids (negatively charged ions), and would not bind potassium (a positively charged ion). Further, since the most common bile acids have molecular weights of at least 375 g/mol, the permeability of a coating for particles to bind bile acids (e.g., charge and pore size) would have been much different than the charge and pore size needed to provide the required potassium permeability to the shell component of the claimed core-shell particles. Also, since Macek's Carbopol coatings are dispersed at low pH and gel at neutral pH, a person skilled in the art would have expected them to disintegrate during residence and passage through the gastrointestinal tract since the pH of the stomach is low and the Carbopol would have dispersed at that low pH. Thus, Macek would not have provided a reason for a skilled person to modify the particles of Notenbomer to arrive at the claimed core-shell compositions because the shell would not have the element of not being disintegrated during residence and passage through the gastrointestinal tract as required by claim 1.

When using Notenbomer as the primary reference, the second step of the *Graham* analysis requires consideration of the differences between the prior art and the claims at issue. The Notenbomer patent discloses core-shell particles having a nucleus and a coating wherein the nucleus is a cation exchange material and the coating comprises a membrane that is permeable for monovalent cations. This coating is disclosed as being more permeable for monovalent cations than for bi- or higher valent cations. Exemplified cation exchange materials are polyphosphate and polystyrene sulfonate resins. Exemplified coatings are cellulose acetate and crosslinked polyethyleneimine. Thus, as the Office admits, the difference between the instant claims and Notenbomer's core-shell particles is the specific polymer coatings.

Because the claimed polymer coatings were not disclosed in the Notenbomer patent, the Examiner has recognized that the pending claims are not anticipated by the Notenbomer patent.

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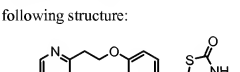
[28] *Id.*

[29] *See* specification at paragraph [0019] and original claim 43.

In formulating a rejection of the claims under § 103(a), the Examiner has found no art that relates to the problem to which the Notenbomer patent relates, but instead has resorted to the Macek et al. patent as disclosing the polymeric coating required in the claims, and forcibly combined the Macek patent with the Notenbomer patent to support the assertion that pretty much any, but especially the claimed pharmaceutical composition comprising core-shell particles, would have been obvious.

It is well established law, that, where the patent at issue claims a chemical compound, the analysis of the *Graham factor* i.e., the differences between the claimed invention and the prior art, turns initially on the structural similarities and differences between the claimed compound and the prior art compounds.[30] Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound.[31] The same is true for a composition.

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[32] the Federal Circuit addressed the obviousness issue for structurally similar chemical compounds. In *Takeda*, the claim at issue recited pioglitazone (5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione) having the following structure:



The ethyl substituent is attached to the 5-position on the pyridyl ring.

Alphapharm filed an ANDA to manufacture and sell a generic version of pioglitazone. According to Alphapharm, Takeda's claimed compound would have been obvious over the prior art compound TZD ("compound b": a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring)[33], having the following structure:

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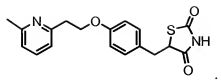
[30] *See Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1377; 81 USPQ2d 1324 (Fed. Cir. 2006).

[31] *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356; 83 USPQ2d 1169 (Fed. Cir. 2007).

[32] 492 F.3d 1350 (Fed. Cir. 2007).

[33] *Id.* at 1354.



Alphapharm argued that one of ordinary skill in the art would select compound b for antidiabetic research and then make "two obvious chemical changes: first, homologation, i.e., replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, 'ring-walking,' or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone."[34]

The district court found, however, that one of ordinary skill in the art would not have selected compound b from the "hundreds of millions" of possible compounds. "[T]he prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research."[35] The Federal Circuit affirmed and held that there was no motivation to select a particular prior art compound (e.g., compound b) from the universe of prior art compounds and even if there was such a motivation, nothing in the prior art would have led a skilled person to modify compound b to arrive at the claimed compound. Thus, when determining the obviousness of new chemical compounds, there must be "some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness."[36]

Once a reason to modify a known compound is found, the skilled person must also have a reasonable expectation that such a modification will be successful or beneficial in some way. In many chemical cases a "reasonable expectation of success" is not always found, as the Federal Circuit stated in *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*[37]

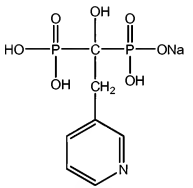
> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. See Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007). ("Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new

[34] *Id.* at 1357.
[35] *Id.* at 1358.
[36] *Id.*
[37] *Eisai Co. v. Dr. Reddy's Laboratories, Inc.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

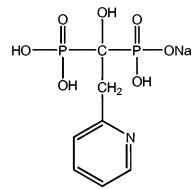
claimed compound."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S. Ct. at 1742. In Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable. (Emphasis added)

As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[38] There is no reason for the forced combination at issue here.

As another instructive example, consider *Procter & Gamble Co. v. Teva Pharmaceuticals*,[39] where risedronate, a bisphosphonate which is a bone resorption inhibitor, was the subject of the challenged claims. Risedronate and its closest prior art compound, 2-pyrEHDP are shown below. Risedronate and 2-pyrEHDP are positional isomers.



risedronate



2-pyrEHDP

Although Teva argued that a chemist would have conceived of the positional isomers, the court held that due to the positional change of the nitrogen atom, the isomers differ in three dimensional shape, charge distribution, and hydrogen bonding properties and hence are not obvious over each other. Further, there was evidence that the bisphosphonate art was unpredictable, so there was no reasonable expectation that a modification would have been successful.

[38] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.
[39] 566 F.3d 989, 90 U.S.P.Q.2d 1947 (Fed. Cir. 2009).

Just like Alphapharm in *Takeda*, the PTO is arguing that it would have been obvious to one of ordinary skill in the art to choose the specific polymeric coatings of Macek from the millions of possible available coatings in the prior art because both references are directed to binding ions in the gastrointestinal tract. As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[40] Although the Office states binding ions in the gastrointestinal tract provides the reason for combining the references, similar to *Ex parte Meagher*, such a general statement for the reason for combining the references does not address the specific claim elements, e.g., why one would select the Macek patent from the multitude of references describing the same coating method.[41] Further, the Office states that the reason to combine the Bogentoft patent is to form a more stable composition. Again, the reason for the combination is so general as to be the reason to combine millions of teachings with the teachings of Notenbomer and/or Macek.

The question is not whether there is a reason to make an improvement. That is essentially always the case. The question is whether there is a reason to make a particular modification, and if so, whether there is any expectation of an improvement.

The Office has not provided a reason for the modification of the coating materials with enough particularity to establish a *prima facie* case of obviousness. Further, there is no reason provided in the cited art or reliance on knowledge in the art that would have led a skilled person to select the core-shell particles from Notenbomer and the polymeric coating from Macek to make pharmaceutical compositions comprising core-shell particles as required by claim 1.

Applicants submit that the PTO is engaging in the exact hindsight bias that the Court has repeatedly urged must be avoided. The PTO has not provided a reason why a skilled person would choose the polymeric coating in Macek. In fact, the Macek polymers would not meet the requirement that the shell not be disintegrated during residence and transit through the gastrointestinal tract because the Carbopol 934 disperses to form a solution at low pH (e.g., in the stomach).

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[40] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

[41] *Ex parte Meagher*, Appeal no. 2008-3613; Application No. 10/380,898 decided September 22, 2008 at page 15 (describing that combining references for the purpose of "obtaining a conversion coating having good corrosion resistance and good top coat adhesion properties-which are likely goals of virtually every conversion coating composition-do not provide the ordinary coating formulations chemist with a reason to systematically vary" the prior art compositions to arrive at the claimed composition.).

Thus, since the problem of Macek is different from Notenbomer's, not only is it not properly combined with Notenbomer, but it does not provide a reasonable expectation that the modified particles would have the claimed elements including shell nondisintegration. Macek is directed to bile acid binders that have a core of an amine polymer and a shell that can be an acrylic acid polymer and provides a palatable composition. An amine polymer core binds anions (e.g., bile acids) and would not be a potassium binding cation exchange polymer as required by the instant claims.

Therefore, the PTO has failed to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. There is simply no reason that a skilled person would have combined Notenbomer and Macek patents to arrive at the claimed invention. Moreover, the core-shell particles taught by the combination of Notenbomer and Macek would not serve the purpose of Notenbomer to provide a composition comprising a nucleus containing a cation exchange material and a coating comprising a membrane permeable to monovalent cations that is essentially not disintegrated during passage through the intestinal tract of humans or animals and is more permeable for monovalent cations than for bi- or higher valent cations.[42] The particle taught by the combination of Notenbomer and the coating of Macek would be disintegrated during passage through the intestinal tract of a human or animal. Thus, the shell of the combined teachings of Notenbomer and Macek would not have been able to bind and remove monovalent cations from the gastrointestinal tract since once the shell dispersed, the cation exchange material would preferentially bind the bi- or higher valent cations.

Further, Bogentoft is cited as evidence that adjusting the coating thickness is well known in the art and the coating thicknesses of Bogentoft would have been selected to form a more stable coating. However, Bogentoft does not provide any further reason why claims 1, 17, 31, 32, 45-56, 58-65, and 67 are obvious over the cited references, since Bogentoft was combined with the Notenbomer and Macek references to provide the element of shell thickness required in claims 22-24 and 68-69.

Applicants submit that the PTO is engaging in the very hindsight bias that the Court has repeatedly urged must be avoided. The PTO has not provided a reason why a skilled person would have chosen the coatings of Macek from the universe of possible coatings. Hence, the

[42] *See* EP App. No. 0 040 590. p. 2, ln. 47-54.

only way that the PTO could arrive at this conclusion is based on the teachings of the instant application while disregarding what the art would have actually led a skilled person to do. Thus, claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 are patentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a).

Claims 22, 23, and 24

Reconsideration is respectfully requested of the rejection of claims 22, 23, and 24 as unpatentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a). Independent claim 1 is summarized above. Claims 22, 23, and 24 further require a shell component about 1 nm to about 50 μm thick, a core shell particle from about 200nm to 2mm in size, and a shell component from about 0.005 microns to about 20 microns thick. Notenbomer does not disclose the thickness of the shells or the core-shell particle size as required by claims 22, 23, and 24, respectively. Thus, Notenbomer does not describe all the elements of claims 22, 23 and 24 because it does not describe the required thickness or the required shell to core weight ratio.

The Bogentoft reference is described above. While the Office states that "it would have been obvious to apply the acrylic polymer to the ionic exchanger resin of the combination in order to provide an even and stable formulation that allowed ions to pass through,"[43] this reason does not place Applicants' invention in the same field as the Bogentoft patent nor does it address the problem disclosed in Applicants' specification or the still different problem discussed in the Notenbomer patent.

As described above, the teachings of Macek are not properly combined with Notenbomer to provide core shell particles with the specific polymer coating to allow exchange of potassium cations and prevent disintegration. The teaching of Bogentoft does not remedy this insufficiency. Moreover, Bogentoft cannot properly be combined with the Notenbomer patent because a skilled person would not have considered the teachings of Bogentoft (directed to encapsulating drugs for release in the lower intestine) when developing core-shell particles that have a shell thickness that increases the amount of potassium bound by the particles. Bogentoft describes a coating that is not used to increase the amount of potassium bound by a polymeric

[43] *See* Office action dated May 4, 2010 at page 5.

core and Bogentoft provides no suggestion that the coatings would perform to solve the problem facing the claimed invention so that the skilled person would use such a coating to modify the particles of Notenbomer. Thus, the two patents are not in the same field of endeavor and do not address the same problem, so they are not analogous art. Also, Bogentoft does not evidence common general knowledge of a person of ordinary skill in the art that would have provided a reason to combine the two patents. As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[44]

Claim 45

Claim 45 is directed to a method of treating an animal subject suffering from renal insufficiency or renal failure, comprising administering to the subject in need thereof an effective amount of a core-shell particle having a core component comprising a potassium-binding cation exchange polymer and a shell polymer being produced by free radical polymerization of an ethylenic monomer.

By rejecting claim 45, the Office simply ignores the requirement that the subject is suffering from renal insufficiency or renal failure as required by claim 45. None of the cited references address this element. As discussed in detail above, this limitation greatly affects how a patient's body chemistry is functioning, and whether the references cited even have a place in the obviousness conversation.[45]

In *Jansen v. Rexall Sundown, Inc.*,[46] a claim directed to a "method of treating or preventing macrocytic-megaloblastic anemia in humans" by "administering a ... vitamin preparation to a human in need thereof...."[47] was construed by the Federal Circuit as follows.

> [T]he claims' recitation of a patient or a human "in need" gives life and meaning to the preambles' statement of purpose. *See Kropa v. Robie*, 187 F.2d 150, 152 [88 U.S.P.Q. 478] (C.C.P.A. 1951) (stating the rule that a preamble is treated as a limitation if it gives "life and meaning" to the claim). The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of the intentional purpose for which the method must be performed.[48]

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[44] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.
[45] *See* Office action dated September 18, 2009 at page 5.
[46] 68 U.S.P.Q.2d 1154, 1158 (Fed. Cir. 2003).
[47] *See id.* at 1155.
[48] *See id.* at 1158.

Thus, the preamble's requirement that the core-shell particles be administered to a patient suffering from renal insufficiency or renal failure is an element that must be present in the cited references in order to negate patentability of claim 45.

Since the preamble must be given patentable weight, the issue is whether it would have been obvious from the cited references to treat a patient suffering from renal insufficiency or renal failure with core-shell particles having a shell with the claimed thickness or core-shell particle size. There can be no basis for inherency where the claim is directed to a method of treating a condition that ordinarily would not have been present in the patients whose treatment is described in the prior art; and there can be no basis for obviousness where the prior art further fails to recognize the potential effect of the treating agent against the condition specified in the claim. As the C.C.P.A. has stated in reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent:

> [Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.[49]

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.[50] Similar to *Shetty*, claim 45 recites a method for removing potassium in a patient in need thereof and suffering from renal insufficiency or renal failure by administering core-shell particles having a shell of the claimed thickness or the core-shell particle size while Notenbomer discloses methods for treating hypertension by administration of core-shell particles and Macek is directed to treating diabetes. The Office has failed to show a reasonable expectation, or some predictability that the composition resulting from the combination of prior art references would

[49] 195 U.S.P.Q. 753 (C.C.P.A. 1977).
[50] *See id.* at 756.

have been effective in treating a patient suffering from renal insufficiency or renal failure. Thus, claim 45 is patentable over the cited references.

Moreover, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.[51] The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to suggest its solution. Similarly, the cited references are concerned with treating hypertension by administration of core-shell particles and treating hypercholesteremia with coated polymers and they fail to suggest to a skilled person that the claimed core-shell particles would have been beneficial to remove potassium from a patient in need thereof and suffering from renal insufficiency or renal failure.

Claim 60

Claim 60 is directed to the method of claim 45 where the animal subject is a human suffering from hyperkalemia. Notenbomer and Bogentoft are described above. The Office asserts that the claimed invention would be obvious from the ion exchange resin of Notenbomer and the coating of Macek because Notenbomer binds excess potassium ions and requires a coating permeable to those ions, and Macek shows coatings used for binding bile in the gastrointestinal tract.[52]

As described above, claim 60 requires the shell component of the core-shell particle to be a crosslinked polymer being produced by free radical polymerization of an ethylenic monomer. Bogentoft describes the coating of pharmaceutical compositions which direct the release into the lower part of the intestines. Further, as described above, the Office has provided no reason why the Bogentoft patent would have been selected from the universe of coated particles to modify the Notenbomer particles. Moreover, although the Office states that it would have been obvious to use the cation exchange polymers to treat hyperkalemia, the Office provides no reason why the polymers of the Macek reference would have been selected from the universe of cation exchange polymers. If it is asserted that these limitations are inherently met by Notenbomer, such an assertion is improper. The *Spormann* court stated that obviousness and inherency are different questions and "[t]hat which may be inherent is not necessarily known. Obviousness

[51] *Ex parte Zbornik*, 109 U.S.P.Q. 508 (B.P.A.I 1956).
[52] *See* Office action dated May 4, 2010 at page 4.

cannot be predicated on what is unknown."[53] Thus, since it is unknown whether the Notenbomer particles would have the claimed elements, the claimed pharmaceutical compositions cannot be obvious from the Notenbomer disclosure and there is no cogent reasoning why a skilled person would combine the teachings from the cited references to arrive at the claimed invention.

Claim 68

Reconsideration is respectfully requested of the rejection of claims 68 and 69 as unpatentable over Notenbomer (EP 0 730 494) in view of Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a). Independent claim 68 is summarized above. Claim 68 generally requires a shell component being prepared from an acrylic or methacrylic monomer and having a particular shell thickness, and a particular core-shell particle size. Notenbomer does not disclose the particular shell monomers, thickness of the shells or the core-shell particle size as required by claims 68 and 69. Thus, Notenbomer does not describe all the elements of claims 68 and 69.

The Macek and Bogentoft references are described above. While the Office states that "it would have been obvious to apply the acrylic polymer [of the Bogentoft patent] to the ionic exchanger resin of the combination in order to provide an even and stable formulation that allowed ions to pass through,"[54] this reason does not place Applicants' invention in the same field as the Bogentoft patent nor does it address the problem disclosed in Applicants' specification or the still different problem discussed in the Notenbomer patent.

As described above, the teachings of Macek are not properly combined with Notenbomer to provide core shell particles with the specific polymer coating to allow exchange of potassium cations and prevent disintegration. The teaching of Bogentoft does not remedy this insufficiency. Moreover, Bogentoft cannot properly be combined with the Notenbomer patent because a skilled person would not have considered the teachings of Bogentoft (directed to encapsulating drugs for release in the lower intestine) when developing core-shell particles that have a shell thickness that increases the amount of potassium bound by the particles. Bogentoft describes a coating that is not used to increase the amount of potassium bound by a polymeric core and Bogentoft provides no suggestion that the coatings would perform to solve the problem

[53] *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966).
[54] *See* Office action dated May 4, 2010 at page 5.

facing the claimed invention so that the skilled person would use such a coating to modify the particles of Notenbomer. Thus, the two patents are not in the same field of endeavor and do not address the same problem, so they are not analogous art. Also, Bogentoft does not evidence common general knowledge of a person of ordinary skill in the art that would have provided a reason to combine the two patents. As *KSR v. Teleflex* and *Takeda v. Alphapharm* emphasize, it is important to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."[55]

In sum, claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 are patentable over Notenbomer (EP 0 730 494) in view Macek et al. (U.S. Patent No. 3,499,960) and Bogentoft (EP 0 040 590) under 35 U.S.C. § 103(a).

[55] *KSR v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, 1396.

VIII. CONCLUSION

For the reasons stated above, Appellants respectfully request that the Office's 35 U.S.C. § 103(a) obviousness rejection of claims 1, 17, 22-24, 31, 32, 45-56, 58-65, and 67-69 be reversed.

The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,

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JSH/clp

IX. CLAIMS APPENDIX

1. An oral or rectal pharmaceutical composition comprising

a pharmaceutically acceptable excipient, and

core-shell particles, said core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer, the shell component comprising a crosslinked synthetic polymer, the synthetic polymer being produced by free radical polymerization of an ethylenic monomer selected from the group consisting of acrylic, methacrylic, styrenic, dienic, vinylic and combinations thereof and being essentially not disintegrated during residence and passage through the gastrointestinal tract of an animal subject.

Claims 2-16. (Canceled)

17. The pharmaceutical composition of claim 1 wherein said core component is physically or chemically attached to said shell component.

Claims 18-21. (Canceled)

22. The pharmaceutical composition or method of claim 1 or 45 wherein said shell component is about 1 nm to about 50 μm thick.

23. The pharmaceutical composition or method of claim 1 or 45 wherein said core-shell particle is about 200 nm to about 2 mm in size.

24. The pharmaceutical composition or method of claim 1 or 45 wherein said shell component is about 0.005 microns to about 20 microns thick.

Claims 25-30. (Canceled)

31. The pharmaceutical composition of claim 1 wherein said shell component is deposited with a coating process.

32. The pharmaceutical composition of claim 1 further comprising an enteric coating.

Claims 33-44. (Canceled)

45. A method of removing potassium ion from a gastrointestinal tract of an animal subject in need thereof and suffering from renal insufficiency or renal failure, the method comprising:

administering to the animal subject suffering from renal insufficiency or renal failure a composition comprising core-shell particles, the core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer, the shell component comprising a polymer being produced by free radical polymerization of an ethylenic monomer,

binding potassium ion with the core-shell particles in the gastrointestinal tract of the animal subject, and

retaining bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastrointestinal tract of the animal subject suffering from renal insufficiency or renal failure, such that potassium ion is removed from the gastrointestinal tract of the animal subject by the core-shell particles to obtain a therapeutic and/or prophylactic benefit.

46. The pharmaceutical composition or method of claim 1 or 45 wherein the core component comprises a crosslinked cation-exchange polymer.

47. The pharmaceutical composition or method of claim 1 or 45 wherein the core component comprises a cation-exchange polymer comprising acidic functional groups.

48. The pharmaceutical composition or method of claim 1 or 45 wherein the core component comprises a cation-exchange polymer comprising functional groups selected from the

group consisting of carboxylate, phosphonate, sulfate, sulfonate, sulfamate and combinations thereof.

49. The pharmaceutical composition or method of claim 45 wherein the shell component comprises a crosslinked polymer.

50. The pharmaceutical composition or method of claim 45 wherein the shell component comprises a crosslinked synthetic polymer.

51. The pharmaceutical composition or method of claim 45 wherein the shell component comprises a polymer produced by polymerization of an ethylenic monomer selected from the group consisting of acrylic, methacrylic, styrenic, dienic, vinylic and combinations thereof.

52. The pharmaceutical composition or method of claim 1 or 45 wherein the shell component comprises a polymer produced by polymerization of a vinylic monomer.

53. The pharmaceutical composition or method of claim 1 or 45 wherein the shell component comprises a polymer produced by polymerization of an acrylic or methacrylic monomer.

54. The method of claim 45 wherein the shell component is essentially not disintegrated during residence and passage of the core-shell particles through the gastrointestinal tract.

55. The pharmaceutical composition or method of claim 1 or 45 wherein the core-shell particles retain at least about 50% of the bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastrointestinal tract.

56. The pharmaceutical composition or method of claim 45 or 67 wherein the core-shell particles retain at least about 75% of the bound potassium ion with the core-shell particles during residence and passage of the core-shell particles through the gastrointestinal tract.

57. (Canceled)

58. The pharmaceutical composition or method of claim 45 or 68 wherein the animal subject is a human suffering from end stage renal disease (ESRD).

59. The pharmaceutical composition or method of claim 45 or 68 wherein the animal subject is a human dialysis patient.

60. The pharmaceutical composition or method of claim 45 or 68 wherein the animal subject is a human suffering from hyperkalemia.

61. The pharmaceutical composition or method of claim 1 or 45 wherein the shell component is hydrophobic.

62. The pharmaceutical composition or method of claim 1 or 45 wherein the core component comprises a crosslinked cation-exchange polymer comprising acidic functional groups, and the shell component comprises a crosslinked synthetic polymer.

63. The pharmaceutical composition or method of claim 62 wherein the shell component is hydrophobic.

64. The pharmaceutical composition or method of claim 62 wherein the shell component comprises a polymer produced by polymerization of a vinylic monomer.

65. The pharmaceutical composition or method of claim 62 wherein the shell component comprises a polymer produced by polymerization of an acrylic or methacrylic monomer.

66. (Canceled)

67. The pharmaceutical composition of claim 1 wherein said core-shell particles bind potassium ion in a gastrointestinal tract of an animal subject suffering from renal insufficiency or renal failure, and retain bound potassium ion during residence and passage of the core-shell particles through the gastrointestinal tract of the animal subject suffering from renal insufficiency or renal failure, such that potassium ion is removed from the gastrointestinal tract of the animal by the core-shell particles to obtain a therapeutic and/or prophylactic benefit.

68. An oral pharmaceutical composition comprising a pharmaceutically acceptable excipient and core-shell particles, said core-shell particles comprising a core component and a shell component, the core component comprising a potassium-binding cation exchange polymer, the shell component comprising a crosslinked polymer produced by polymerization of an acrylic or methacrylic monomer wherein said shell component is about 0.005 microns to about 20 microns thick and said core-shell particle is about 200 nm to about 2 mm in size and the shell component being essentially not disintegrated during residence and passage through the gastrointestinal tract of an animal subject.

69. The pharmaceutical composition of claim 1 or 68 wherein the oral pharmaceutical composition is in the form of a powder, tablet, capsule, or emulsion.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None.